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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

STEADMAN, DAVID J

ART UNIT PAPER NUMBER

1652

DATE MAILED: 08/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/997,664

Applicant(s)

BEN-BASSAT ET AL.

Examiner

David J Steadman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 July 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12-17 and 19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12-17 and 19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 7/6/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

- [1] Claims 12-17 and 19 are pending in the application.
- [2] Applicants' amendment to the claims, filed July 06, 2004, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.
- [3] Applicants' amendment to the specification, filed July 06, 2004, is acknowledged.
- [4] Receipt of Form PTO-1449, filed July 06, 2004, is acknowledged.
- [5] Receipt of a request to change inventorship, filed July 06, 2004, is acknowledged.
- [6] Receipt of a declaration of deposit, filed July 06, 2004, is acknowledged.
- [7] Applicant's arguments filed June 23, 2004 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.
- [8] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Information Disclosure Statement

- [9] With the exception of "PCT/US98/12072, No Reference Included," all references cited in the information disclosure statement filed March 20, 2002 have been considered. A copy of Form PTO-1449 is attached to the instant

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Office action. Reference "PCT/US98/12072, No Reference Included" has not been considered as the examiner cannot find a copy of the cited reference in the application.

Correction of Inventorship

[10] In view of the papers filed July 06, 2004, the inventorship in this nonprovisional application has been changed by the deletion of Katharine J. Gibson.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Oath/Declaration

[11] In view of the papers filed July 06, 2004 to delete Katharine J. Gibson as co-inventor, the objection to the declaration as set forth in item [7] of the Office action mailed February 05, 2004 is withdrawn.

Specification/Informalities

[12] In view of the amendment to the specification, the objections to the specification as set forth in items [8]-[10] of the Office action mailed February 05, 2004 are withdrawn.

Claim Rejections - 35 USC § 112, Second Paragraph

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[13] In view of the amendment to the claims, the rejection of claims 12-17 and 19-20 under 35 U.S.C. 112, second paragraph, to the extent the rejection applies only to items [12]-[13] and [15]-[16] of the Office action mailed February 05, 2004, is withdrawn.

[14] The rejection of claims 12-17 and 19 as being indefinite in the recitation of "genes encoding... ..TmoX... ..activities" is maintained for the reasons of record as set forth in item [14] of the Office action mailed February 05, 2004 and for the reasons stated below.

[15] RESPONSE TO ARGUMENTS: In response to the examiner's request for applicants to direct the examiner's attention to a description of the activity of a TmoX polypeptide, applicants point to pp. 43-44 of the specification. However, this portion of the specification fails to define the activity of a TmoX polypeptide and, as such, the intended activity exhibited by a TmoX polypeptide is unclear. While it is acknowledged that the specification states that TmoX shares identity with TodX and suggests a biological activity of a TodX polypeptide, there is no indication that the activity of TmoX is similar to or is identical to that of a TodX polypeptide. While other polypeptide activities are recited in claim 12, i.e., toluene-4-monooxygenase, PcuR (defined as a transcriptional activator of the pcu operon), para-cresol methylhydroxylase, TmoST polypeptides (defined in the specification as transcriptional activators of the tmo operon), and para-hydroxybenzoate dehydrogenase, these activities are either well-known in the art or are defined in the specification such that one of skill in the art can distinguish

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the scope of these activities from others. It is suggested that applicants clarify the meaning of a TmoX activity.

[16] Claims 12-17 and 19 are rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 12 (claims 13-17 and 19 dependent therefrom) is indefinite in the recitation of "PcuR" and "TmoST polypeptides" as it is unclear from the specification and the claims as to the identifying characteristics of genes encoding "PcuR" and "TmoST polypeptides" that distinguish such genes from others. The specification teaches properties of "PcuR" and "TmoST polypeptides," i.e., transcriptional activator of the pcu operon or transcriptional activators of the tmo operon, respectively, but fails to define the characteristics that are necessary for inclusion of a gene encoding "PcuR" or "TmoST polypeptides" that is distinct in sequence from other genes encoding polypeptides having similar activities.

[b] Claim 12 (claims 13-17 and 19 dependent therefrom) is indefinite as it is unclear as to the polynucleotides with which the bacterial host cell has been transformed. While part (a)(iii)(2) of claim 12 recites specific genes that the transformed host cell comprises, it is unclear as to whether the transformed host cell is transformed with all of these genes, some of these genes, or if it endogenously comprises these genes and is transformed with some other genes that are not recited in the claim. It is suggested that applicants clarify the meaning of the claim.

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[c] Claim 12 (claims 13-17 and 19 dependent therefrom) is indefinite in the recitation of "compounds that are similar in chemical structure to toluene and the intermediates of the toluene monooxygenase pathway." It is unclear from the claims and the specification as to how "similar" a compound must be to toluene and the intermediates of the toluene monooxygenase pathway in order to be encompassed within the scope of recited aromatic organic intermediates. As such, it is unclear as to the scope of aromatic organic substrates that can be used in the production of para-hydroxybenzoate. It is suggested that applicants specifically identify those aromatic organic substrates that are intended to be encompassed by the term "compounds that are similar in chemical structure to toluene and the intermediates of the toluene monooxygenase pathway."

[17] RESPONSE TO ARGUMENTS: To the extent applicants' arguments apply to the instant rejection, these arguments are addressed below. Applicants argue the definition of "compounds that are similar in chemical structure to toluene and the intermediates of the toluene monooxygenase pathway" can be found at page 27, lines 5-7 of the specification and that based on this definition, a skilled artisan can readily identify such compounds. Applicants' argument is not found persuasive.

As stated above, it is unclear as to how "similar" to toluene or intermediates of the TMO pathway a compound must be to be included within the scope of such "compounds." Consequently, the term is indefinite at least for the reasons stated above.

Claim Rejections - 35 USC § 112, First Paragraph

[18] The written description rejection of claims 12-17 and 19 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item [17] of the Office action mailed February 05, 2004 and for the reasons stated below.

[19] RESPONSE TO ARGUMENTS: Applicants argue that the genus of transformants of claim 12 is defined as the species encompassed by the genus are prokaryotes that are genetically well-characterized and are capable of transformation by well-known techniques. Applicants argue the substrates and enzymes of the invention are commercially available or are reproducible and their use in the claimed method would be routine and predictable. Applicants argue that three different representative species of the recited genus of transformants. Applicants argue the disclosed representative species, in view of the state of the art at the time of the invention, support the entire genus of recited transformants. Applicants' argument is not found persuasive.

The examiner maintains the position that the disclosed representative species fail to represent all species of transformed bacterial hosts and aromatic organic compounds that can be converted into para-hydroxybenzoate, specifically those compounds that are "similar in chemical structure to toluene" and intermediates of the TMO pathway. These features of the claimed invention appear to be essential or critical to the claimed invention and thus require adequate written description. However, the recited genus of compounds that are

"similar in chemical structure to toluene" and intermediates of the TMO pathway that can be converted into para-hydroxybenzoate and the recited genus of transformed bacterial host cells encompasses species that are widely variant. In this case, the recited genus of aromatic organic substrates that are "similar in chemical structure to toluene" and intermediates of the TMO pathway that can be converted into para-hydroxybenzoate is widely variant, encompassing all compounds having an undefined similarity to toluene and intermediates of the TMO pathway.

Also, the recited genus of transformed bacterial host cells encompasses species that are widely variant, including species transformed with any gene from any source encoding toluene-4-monooxygenase, TmoX (whatever the activity of this polypeptide may be as the specification fails to define such), PcuR (defined as a transcriptional activator of the pcu operon), para-cresol methylhydroxylase, TmoST polypeptides (defined as transcriptional activators of the tmo operon), and para-hydroxybenzoate dehydrogenase, as recited in part (iii)(2) of claim 12, including those wild-type genes from any source and all mutants and variants thereof. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus and that when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the disclosed species fail to represent all species of aromatic organic compounds that can be converted into para-hydroxybenzoate and further fails to represent all species of transformed bacterial host cells. As such, the

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specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[20] In view of applicants' submission of a declaration of biological deposit of plasmid pCM4, the enablement rejection of claim 19 under 35 U.S.C. 112, first paragraph, as set forth in item [18] of the Office action mailed February 05, 2004, is withdrawn. Applicants are advised that 37 CFR § 1.809(d) requires that "[f]or each deposit made pursuant to these regulations, the specification shall contain: (1) The accession number for the deposit; (2) The date of the deposit; (3) A description of the deposited biological material sufficient to specifically identify it and to permit examination; and (4) The name and address of the depository" and that 37 CFR § 1.809(e) states that "[a]ny amendment required by paragraphs (d)(1), (d)(2) or (d)(4) of this section must be filed before or with the payment of the issue fee." It is suggested that applicants incorporate the appropriate information required by 37 CFR § 1.809(d) into the specification.

[21] The scope of enablement rejection of claim(s) 12-17 and 19 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in item [20] of the Office action mailed February 05, 2004 and for the reasons stated below.

[22] RESPONSE TO ARGUMENTS: Applicants argue the amended claims define the scope of the invention with specificity and that the state of the art regarding recombinant DNA technology, screening methods, culture optimization, and substrate utilization is well developed and thus such methods would

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allegedly require only routine experimentation and that the scope of the claims is not overly broad and would not require undue experimentation.

Specifically addressing the scope of aromatic substrates to be used in the production of para-hydroxybenzoate, applicants argue claim 12 has been amended to recite a genus of substrates that are clearly defined and readily identifiable and that testing the members of this genus would be routine.

Specifically addressing the scope of bacterial transformants, applicants argue the specification provides two different ways for a cell to lack para-hydroxybenzoate hydroxylase activity, allegedly demonstrating that obtaining such cells is within the ability of a skilled artisan without undue experimentation. Applicants argue that it is routine experimentation to identify homologues of the recited genes as these methods are well known and established and such genes can be isolated and screened for those that can be used in the claimed invention using methods disclosed in the specification and methods that are known in the art without undue experimentation. Applicants' argument is not found persuasive.

In response to applicants' argument addressing the scope of aromatic organic substrates, contrary to applicants' assertion, the scope of aromatic organic compounds that "are similar in chemical structure to toluene" and intermediates the TMO pathway are not clearly defined either in the specification or the prior art and are not clearly identifiable to one of skill in the art. Instead, the claimed invention encompasses the conversion of any compound that one may deem "similar in chemical structure" to toluene or intermediates of the TMO pathway. As the specification fails to define those structural characteristics of an

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aromatic organic compound that would constitute a compound being "similar in chemical structure" to toluene or intermediates of the TMO pathway. As such, the claims encompass the conversion of a vast number of aromatic organic substrates to para-hydroxybenzoate. However, the specification provides working examples of the bio-conversion of only toluene, para-cresol, para-hydroxybenzyl alcohol, and para-hydroxybenzaldehyde to para-hydroxybenzoate. In view of the lack of guidance and working examples, it cannot be predicted a priori which of the vast number of compounds encompassed by the scope of the claims are useful for the production of para-hydroxybenzoate. Thus, one must screen each and every compound that one considers "similar in chemical structure" to toluene or intermediates of the TMO pathway for those that can be converted into para-hydroxybenzoate. In view of the breadth of the claims, the lack of guidance and working examples, the high level of unpredictability, and the significant amount of experimentation required to make the full scope of claimed methods, it is the examiner's position that undue experimentation is required to practice the claimed invention.

In response to applicants' argument addressing the scope of bacterial transformants, it is noted that scope of claimed bacterial transformants is not limited to those that do not endogenously express para-hydroxybenzoate hydroxylase. Thus, the claims encompass bacteria that do express para-hydroxybenzoate hydroxylase, wherein the activity of this polypeptide has been disrupted by any method, not just gene knockout by homologous recombination as disclosed in the specification. Even assuming arguendo the claims were

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limited to those bacterial transformants whose para-hydroxybenzoate hydroxylase activity was abolished by homologous recombination, the specification fails to provide guidance for knocking out a para-hydroxybenzoate hydroxylase gene in all bacteria. Homologous recombination requires knowledge of a gene's nucleic acid sequence and, as gene sequences are rarely identical between all species of bacteria, one of skill in the art would recognize the high level of unpredictability that the sequence of a single bacterial gene will be useful for knocking out all other bacterial genes.

Further, regarding the isolation of homologous genes, while methods for isolating homologous genes were known in the art at the time of the invention, it is noted that it is not routine in the art to isolate all homologous genes from all bacteria, including mutant and variant genes, as encompassed by the claims, particularly in view of the lack of guidance in the specification regarding regions of nucleic acid sequence within the gene that are likely to be conserved throughout all species such that a skilled artisan would have a reasonable expectation of success for isolating all other homologous genes. As such a level of experimentation that is not routine is required to make all transformants to practice the full scope of the claimed invention. Herein the guidance provided in the specification, i.e., methods for isolating homologous genes and screening for the desired activity, provides only a starting point for further research such that one may be able to make the full scope of the claimed invention. In view of the breadth of the claims, the lack of guidance and working examples, the high level of unpredictability, and the significant amount of experimentation required to

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make the full scope of claimed methods, it is the examiner's position that undue experimentation is required to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

[23] Claim(s) 12-13 and 15-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Miller et al. (Green Chemistry 1:143-152; cited in the IDS filed July 06, 2004). Claims 12-13 and 15 are drawn to a method for the production of PHBA using a transformed bacterial host lacking a para-hydroxybenzoate hydroxylase activity and comprising genes encoding toluene-4-monooxygenase, TmoX, PcuR, para-cresol methylhydroxylase, TmoST polypeptides, and para-hydroxybenzoate dehydrogenase.

Miller et al. teach a method for bioconversion of toluene and para-cresol to PHBA using a P. putida host cell deficient in para-hydroxybenzoate hydroxylase

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activity and comprising genes for recombinant expression of toluene-4-monooxygenase, para-cresol methylhydroxylase, and para-hydroxybenzoate dehydrogenase (p. 143, summary and p. 144, left column). Miller et al. teach that various amounts of para-cresol were added for the bioconversion, including para-cresol at 50 ppm (p. 146, Figure 3). This anticipates claims 12-13 and 15 as written.

While Miller et al. are silent as to the expression of TmoX, PcuR, and TmoST polypeptides, these polypeptides are endogenously expressed by P. putida.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

[24] Claim(s) 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Miller et al. Claim 14 limits the carbon source of claim 12 to glucose.

Miller et al. disclose the teachings as described above. Miller et al. teach the use of glutamate as a fermentable carbon source in their method. Miller et al. do not teach using glucose as a fermentable carbon source in their bioconversion method.

At the time of the invention, it was well-known in the art to use any of a number of fermentable carbon sources for the culturing of P. putida, including glucose.

Therefore, it would have been obvious to one of ordinary skill in the art to replace glutamate with glucose as a fermentable carbon source in the method of Miller et al. One would have been motivated to replace glutamate with glucose as glucose is equivalent to glutamate as a carbon source for the culturing of P. putida. One would have a reasonable expectation of success for practicing the method of Miller et al. using glucose as a carbon source because glucose is a carbon source that can support the growth of P. putida. Therefore, claim 14, drawn to a method for the production of PHBA would have been obvious to one of ordinary skill in the art.

Provisional Rejection - Double Patenting

[25] The provisional double patenting rejection of claims 12-17 and 19 over claims 14, 16, 18, 22-23 and 25-26 of copending US Application 10/464,952 is maintained for the reasons of record as set forth in item [21] of the Office action mailed February 05, 2004 and the reasons stated below.

[26] RESPONSE TO ARGUMENTS: Applicants argue claims 19-20 have been canceled, thus rendering the provisional rejection of these claims moot.

Addressing the remaining claims, applicants argue that this is only a provisional rejection and if the claims of Application '952 are allowed at the time of allowance

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of the instant application, applicants will submit, if appropriate, a terminal disclaimer.

It is noted that claim 19 has not been canceled by the instant amendment and is currently pending, thus the provisional rejection of this claim is maintained. For the reasons set forth in the previous Office action, claims 12-17 and 19 are obvious over claims 14, 16, 18, 22-23, and 25-26 of Application '952.

[27] It is noted that applicants address claims 1-103 of a '797 application (see page 14, bottom). The examiner has made no mention of a '797 application in the instant rejection. As such, applicants' argument addressing the '797 application does not appear to be intended to address the instant rejection and instead appears to be an editing error.

[28] It is further noted that in a previous Office action, the examiner rejected claims 12-17 and 19-20 as being obvious over claims 14, 16-19, and 22-26 of Application '952. However, it is noted that claims 1-11, 17, 19, and 24 of Application '952 have been canceled. Thus, the provisionally rejected claims of Application '952 included in the instant provisional double patenting rejection have been updated to remove those claims of Application '952 that have been cancelled.

Conclusion

[29] Status of the claims:

- Claims 12-17 and 19 are pending.
- Claims 12-17 and 19 are rejected.

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- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (571) 273-0942. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

Patent Examiner

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DS 08-09-04